

Treatment adherence in multiple sclerosis: association with emotional status, personality, and cognition

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Abstract The purpose of the present study was to prospectively examine the association between treatment adherence and common neuropsychiatric symptoms in multiple sclerosis (MS). Patients underwent a thorough psychiatric and neuropsychological evaluation at the outset of the study. Patient adherence to disease modifying therapies was then tracked for 8 weeks using self-report, a medication diary, and an electronic monitoring device that recorded needle disposals. Results indicated that MS patients with current mood or anxiety disorders were almost five times as likely as MS patients with no psychiatric diagnosis to exhibit problems adhering to their disease modifying therapies. Poor adherence was also associated with memory difficulties, anxiety, depression, neuroticism, and low conscientiousness. Findings highlight the importance of conducting a thorough psychiatric and neuropsychological evaluation when clinicians suspect poor adherence to disease modifying therapies. Pharmacological or psychotherapeutic treatment of mood/anxiety disorders, use of scheduled reminders, and/or increased organization and structure may lead to improved treatment adherence in MS.

Keywords Multiple sclerosis · Adherence · MEMS · Cognition · Memory · Depression · Anxiety

Introduction

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system that has significant cognitive and emotional sequelae (Arnett 2003). More than 50% of MS patients experience problems with memory, executive functions, attention, or speed of information processing (Rao et al. 1991a, b). Point prevalence rates for mood disorders among MS patients range from 14 to 57 percent (Mohr and Cox 2001). In addition, roughly 35% of MS patients endorse chronic worry and lifetime prevalence for generalized anxiety disorder in MS has been estimated at 20% (Bruce and Arnett 2009; Korostil and Feinstein 2007). Personality changes, including increased neuroticism and decreased empathy, agreeableness, and conscientiousness have also been observed (Benedict et al. 2001).

MS-related cognitive and emotional difficulties are known to be associated with problems managing independent activities of daily living, poorer vocational status, and reduced quality of life (Benedict et al. 2005; Higginson et al. 2000; Rao et al. 1991a, b). However, no studies have thoroughly examined the association between cognitive and emotional changes in MS and treatment adherence. The purpose of the present study was to examine the association between prospective medication adherence and common cognitive, emotional, and personality sequelae of MS.

The World Health Organization has suggested that improved treatment adherence would have a larger impact on society and health than most therapeutic advances (WHO 2003). Across multiple non-MS disease groups, between 25 and 50% of patients do not properly adhere to their

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prescribed treatment regimens (Bosworth 2006). Poor medication adherence is common among patients with depression, anxiety, diabetes, HIV, coronary artery disease, asthma, and various types of dementia (Altice and Friedland 1998; Brauner et al. 2000; Cramer 2004; Newby et al. 2006; Pampallona et al. 2002; Stein et al. 2006; Wetherell and Unutzer 2003). These adherence difficulties are associated with increased patient morbidity, poorer quality of life, and increased financial strain on health care institutions (Van Houtven et al. 2006).

When compared to other patient populations, patients with MS may be at increased risk of poor long-term adherence. Adherence may be reduced in diseases with waxing and waning courses and patients with relapsing-remitting MS frequently experience periods of relative disease inactivity. It is also well established that patients with low conscientiousness, cognitive difficulties, and emotional problems are especially likely to have problems following prescribed treatment regimens (Albert et al. 2003; Edwards et al. 2009; Insel et al. 2006; Stilley et al. 2004). Given the magnitude of commonly experienced cognitive, personality, and emotional symptoms, MS patients would be expected to have associated problems with treatment adherence. Despite this, no studies have thoroughly examined the association between neuropsychiatric symptoms and long-term treatment adherence in MS.

Several injectable disease modifying therapies have been shown to reduce exacerbations, the formation of brain lesions, and/or disease progression in relapsing-remitting MS, including interferon beta 1a/b, mitoxantrone, and glatiramer acetate (Goodin 2008). Studies that have examined treatment adherence to disease modifying therapies have typically focused exclusively on retrospective self-report and/or imprecise measures of treatment discontinuation (Berger et al. 2004; Fraser et al. 2004; Haas and Firzlaiff 2005; Milanese et al. 2003; Mohr et al. 2001; O'Rourke and Hutchinson 2005; Portaccio et al. 2008; Rio et al. 2005; Ruggieri et al. 2003; Tremlett and Oger 2003). Published discontinuation rates for disease modifying therapies range between 10 and 45%. Among other factors, these studies suggest that treatment discontinuation is related to lower education, increased disability, perceived lack of efficacy, lack of physician support, medication side-effects, and hopelessness.

Only one study has examined variance in long-term use of disease modifying medications in MS (Turner et al. 2007). In this study, poor medication adherence was associated with a lack of perceived benefit. Medication adherence was not consistently associated with list learning or demographic variables. A primary weakness of the study included the exclusive reliance on retrospective self-reports, which may over-estimate adherence due to factors associated with social desirability (Bruce et al. 2010). Other

weaknesses included the use of a mostly male participant group and the absence of a thorough standardized assessment battery measuring cognitive and emotional status.

Given the known effectiveness of disease modifying therapies, an increased understanding of factors that contribute to treatment adherence in MS may help clinicians craft individually tailored treatment plans that boost adherence and therefore reduce MS relapses. The purpose of the current study was to examine the association between baseline neuropsychiatric functioning and multiple measures of longitudinal treatment adherence in MS. Unlike previous studies in MS that have relied solely on retrospective self-reports, the current study employed adherence diaries and a state-of-the-art electronic monitoring system to measure subtle aspects of prospective treatment adherence. In addition, the present study employed a thorough psychiatric interview and comprehensive neuropsychological battery. We hypothesized a priori that poor medication adherence in MS would be associated with baseline cognitive difficulties, emotional disturbances, and low levels of conscientiousness.

Method

Participant recruitment

Relapsing-remitting MS patients were recruited through a large MS specialty clinic associated with the University of Kansas Medical Center. As compensation for their participation, patients were paid \$125. Inclusion criteria included (1) No current alcohol/drug abuse; (2) no nervous system disorder other than MS; (3) no relapse and/or corticosteroid use within 4 weeks of assessment; (4) absence of severe physical/motor/sensory/neurological impairment that would make participation in the study insurmountable; (5) use of a self-injected disease modifying therapy for at least 2 months; (6) no assistance taking disease modifying therapies; and (7) no history of learning disability. Furthermore, to ensure that patients were not suffering from a subtle comorbid degenerative neurologic disorder, only patients less than 61 years of age were included. Initially, only participants taking glatiramer acetate were accepted into the study. As 20 mg glatiramer acetate is injected once daily, this criteria was established to maximize the number of injection events during the course of this 2 month long prospective pilot study. The study was eventually opened to patients taking interferon beta 1a (30 mcg injected once weekly) and interferon beta 1b (.25 mg injected once every other day). Each patient was diagnosed as having MS based on established criteria by a board-certified neurologist who also assessed disease course based on Lublin & Reingold criteria, and rated patients on Kurtzke's Expanded

Disability Status Scale (Kurtzke 1983; Lublin and Reingold 1996; Polman et al. 2005).

Procedure

Upon acceptance into the study, patients were asked how frequently they missed doses during the last 2 month period. Next, patients completed questionnaires, a psychiatric interview, and a battery of neuropsychological tests. Treatment adherence was then monitored prospectively for 8 weeks. Patients were given an electronic monitoring cap (Medication Event Monitoring System; MEMS, AARDEX) and a plastic container to use for needle disposal. Participants were instructed to throw their needle away in the container and re-fasten the cap after each self-injection. In addition, patients were instructed to employ and return adherence diaries, recording each time they self-injected during the same 8-week period. Finally, upon completion of the study, patients reported how many doses of their medication they missed during the same prospective 8-week period (see Fig. 1). All procedures were approved by the University of Missouri-Kansas City and University of Kansas Medical School institutional review boards.

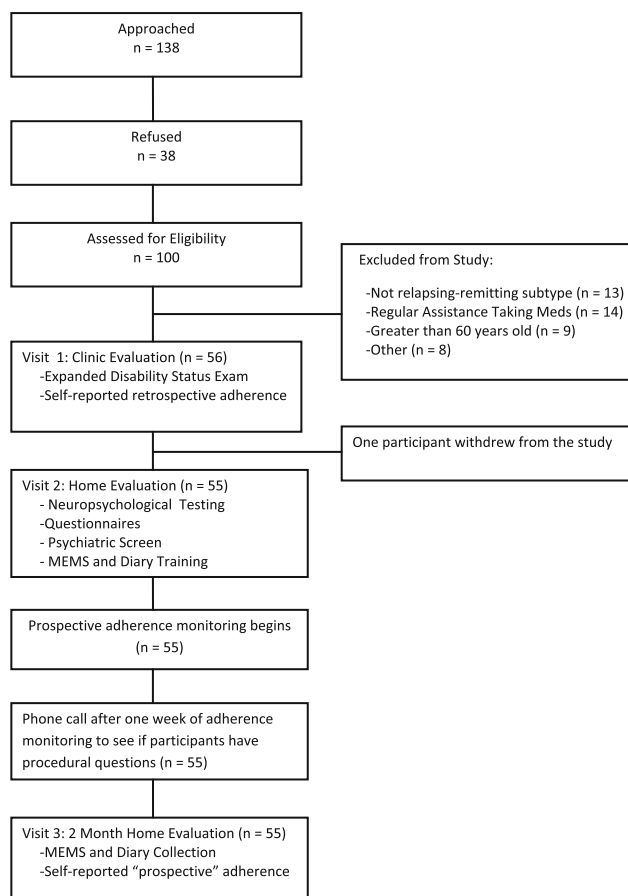


Fig. 1

Measures

Adherence

Medication event monitoring system (MEMS; AARDEX) Electronic adherence was assessed using needle disposal bottles fitted with MEMS caps. Participants were instructed to discard their disease modifying therapy needles in the sharps container after each injection. The MEMS caps recorded the exact time and date for each needle disposal. Upon completion of the study, data from MEMS caps were downloaded using Powerview software (AARDEX). The variable of interest for this study was the percentage of days that participants were not covered by their disease modifying therapy. For instance, each day that a participant missed a dose of glatiramer acetate (prescribed 20 mg once daily) was counted as one day of nonadherence. Similarly, 4 days in between interferon beta -1b doses (prescribed .25 mg every other day) was counted as 3 days of nonadherence and 13 days between interferon beta-1a doses (30 mcg once weekly) was counted as 7 days of nonadherence. Patients were assigned to categorical groups based on the average percentage of medication missed for the two measures documenting poorest adherence.

Adherence diary Each participant was provided with a calendar-style diary in which they recorded the time and date of each injection over the 8 week period. The dependent variable for the current study was calculated in the same manner as described above for MEMS.

Self-reported adherence Self-reported adherence to disease modifying therapy was measured retrospectively at the outset of the study, and then again upon the completion of the 8-week study period. Participants reported the number of doses they believed they missed in the 8-week period prior to the study (retrospective self-report), and then during the 8-week period of the study (prospective self-report). The dependent variable was the percentage of self-reported missed doses.

Emotional and personality functioning

Beck Depression Inventory—Fast Screen (Beck et al. 2000) The Beck Depression Inventory—Fast Screen is a self-report depression questionnaire that has been validated for use among patients with MS (Benedict et al. 2003). This measure demonstrated good internal reliability in this sample (Chronbach's alpha = .85) and has been shown to be reliable and valid in numerous patient populations (Beck et al. 2000).

Trait subscale of the State-Trait Anxiety Inventory (Spielberger 1983) The trait subscale of the State-Trait Anxiety Inventory is a self-report questionnaire designed to assess global anxiety. The widely used questionnaire demonstrated good internal reliability in this sample (Chronbach's $\alpha = .93$).

Mini International Neuropsychiatric Interview (Sheehan et al. 1998) The Mini International Neuropsychiatric Interview is a semi-structured psychiatric interview that conforms to DSM-IV standards for the diagnosis of mental disorders. The dependent variable was the total number of mood and anxiety diagnoses.

Modified Fatigue Impact Scale (Fisk et al. 1994) We employed the five-item version of the Modified Fatigue Impact Scale. Patients were asked to rate how much their fatigue had impacted them over the previous 4 weeks on a five-point scale. This version of the Fatigue Impact Scaled demonstrated good internal reliability in this sample (Chronbach's $\alpha = .85$).

NEO Five Factor Inventory (Costa and McCrae 1992) A self-report questionnaire designed to assess the big five traits of personality: neuroticism, openness, agreeableness, conscientiousness and extraversion. Published Chronbach's alphas for these subscales range from acceptable (.68; agreeableness) to good (.86; conscientiousness).

Cognitive functioning

Symbol Digit Modalities Test, Oral Form This test of information processing speed requires participants to quickly say a number that matches a corresponding symbol (Smith 1982). The dependent variable was the total number of correct responses in 90 s.

Letter Number Sequencing (Wechsler 1997) This test measures working memory and requires examinees to simultaneously recall and arrange a series of orally presented numbers and letters. The dependent variable was total correct trials.

Wisconsin Card Sorting Test (Grant and Berg 1948) This test of executive functioning requires participants to solve a novel problem and demonstrate flexible thinking. For this computerized 64-card version of the task we examined the number of correct responses.

Stroop Color-Word Trial (Stroop 1935) This test measures executive functioning and requires participants to inhibit a natural response (reading a word) and replace it with another response (saying a color). The dependent variable was the number of correct responses in 45 s.

Auditory Verbal Learning Test (Lezak 1995) This test of verbal memory involves participants learning and then recalling a list of unrelated words. An abbreviated version of the test was employed for the present study that included three learning trials and a delayed recall trial.

Memory for Intentions Screening Test (Woods et al. 2008) This standardized test of prospective memory, or remembering to remember, involves patients being asked to generate verbal and physical responses after a time delay or in response to a visual event. An abbreviated version of the test was used that consisted of two event-based and two time-based tasks.

Physical functioning

Expanded Disability Status Scale The Expanded Disability Status Scale is a measure of MS disease progression and neurological impairment. It is commonly used in both clinical practice and MS research in order to quantify the disability associated with MS (Kurtzke 1983).

Data analytic plan

The primary aim of the present study was to examine the relationship between adherence and neuropsychiatric functioning in MS. The results section is structured to systematically investigate emotional, personality, and cognitive factors associated with adherence to disease modifying therapies. Mann–Whitney U tests were used to examine adherence differences between patients with and without a current DSM-IV mood and/or anxiety disorder. Spearman correlations were then employed to examine the association between adherence and self-reported anxiety, depression, and fatigue. Spearman correlations were also employed to examine the association between adherence and personality variables. Next, Spearman correlations were used to examine the association between adherence and tests of memory, attention, and executive functioning. Finally, MS patients were split into variable/poor and good/adequate adherence groups. A Chi-square analysis and *t*-tests were employed to examine between group differences in emotional, personality, and cognitive functioning.

Results

Preliminary analyses

Fifty-five patients with relapsing-remitting MS were included in the study. MS patients were predominantly females (89.1%). The group was primarily Caucasian (90.9%) with a small number of African-Americans (3.6%), Latinas (3.6%) and people of unspecified ethnicity (1.8%). The mean $\pm$ SD age was 43.36 ± 8.43 years with 14.59 ± 1.69 years of education. Diagnosis duration was 8.51 ± 5.99 years and the mean Expanded Disability Status Scale score was 2.19 ± 1.12 . The mean length of current disease modifying therapy use was 5.72 ± 3.49 years. Forty-five patients were taking glatiramer acetate, three were taking interferon 1a and seven were taking interferon 1b. Patients were prospectively monitored by MEMS and the medication diary for an average of 60.64 ± 5.10 and 61.96 ± 5.56 days, respectively. The average percentage of days not covered by medication during the study according to MEMS and medication diary was 6.98 ± 10.62 and 5.85 ± 9.42 days, respectively. For the 8 weeks prior to the study, participants reported missing 6.07 ± 15.25 percent of their prescribed doses. During the course of the study, participants reported missing 4.48 ± 9.18 percent of their prescribed doses. Overall, 18% of patients ($n = 10$) exhibited poor adherence, missing more than 20% of their prescribed medication. An additional 9% of patients ($n = 5$) exhibited variable adherence, missing between 10 and 20% of their prescribed medication. As expected, all

measures of adherence were highly correlated (all r values between .67 and .93). Adherence was not significantly related to age, education, or overall disability.

Emotion and adherence

Sixteen participants (29.1%) met criteria for one or more current anxiety or mood disorders. Diagnoses included generalized anxiety disorder ($n = 9$), major depression ($n = 5$), agoraphobia ($n = 3$), obsessive compulsive disorder ($n = 3$), panic ($n = 1$), and dysthymia ($n = 1$). Additionally, participants had a history of a manic ($n = 2$) or hypomanic episode ($n = 3$). As seen in Table 1, patients with at least one emotional disorder exhibited significantly worse adherence. As shown in Table 2, retrospective self-report ($r = .56$, $P < .001$), prospective self-report ($r = .49$, $P < .001$), electronic monitoring ($r = .46$, $P < .001$), and diary records ($r = .50$, $P < .001$) were all significantly associated with the number of patients' mood and anxiety disorders. Worse retrospective self-reported adherence was significantly associated with increased fatigue ($r = .29$, $P < .05$) and anxiety ($r = .38$, $P < .01$). Worse adherence as measured by diary records was significantly associated with increased anxiety ($r = .29$, $P < .05$), but not measures of fatigue or depression.

Personality and Adherence

As shown in Table 2, worse retrospective self-reported adherence was associated with increased neuroticism

Table 1 MS patients with psychiatric illness exhibit poorer adherence to disease modifying therapies

% Days missing doses	No psychiatric diagnosis ($n = 39$)				Current psychiatric diagnosis ($n = 16$)				Mann–Whitney U	Z	P
	Mean	SD	Median	Mean rank	Mean	SD	Median	Mean rank			
Retrospective self-report	3.30	9.06	0.00	22.47	12.83	23.66	7.14	41.47	96.50	−4.20	<.001
Prospective self-report	1.46	2.55	0.00	22.74	12.14	14.42	8.92	37.80	123.00	−3.54	<.001
Electronic monitoring	3.78	8.07	1.41	23.56	14.78	12.23	12.11	38.81	139.00	−3.31	.001
Diary records	2.68	5.33	0.00	22.96	14.10	12.57	10.34	39.30	115.50	−3.62	<.001

Table 2 Spearman correlations between adherence and emotional/personality variables

	# Psych. diagnoses	BDI	MFIS	STAI	NEO-C	NEO-N	NEO-E	NEO-O	NEO-A
Retrospective self-report	.56**	.25	.29*	.38**	−.47**	.32*	.01	.36**	−.11
Prospective self-report	.49**	.18	.13	.24	−.31*	.22	−.05	.19	−.21
Electronic monitoring	.46**	.20	.12	.25	−.22	.21	.08	.13	−.08
Diary records	.50**	.22	.14	.29*	−.35**	.24	.04	.10	−.15

* = $P < .05$, ** = $P < .01$

Psych. Diagnosis number of DSM-IV psychiatric disorders, *BDI* Beck Depression Inventory–Fast Screen, *MFIS* Modified Fatigue Impact Scale, *STAI* Trait subscale of the State Trait Anxiety Inventory, *NEO-C* Conscientiousness Scale of the NEO-FFI, *NEO-N* Neuroticism scale of the NEO-FFI, *NEO-E* Extroversion scale of the NEO-FFI, *NEO-O* Openness scale of the NEO-FFI, *NEO-A* Agreeableness Scale of the NEO-FFI

Table 3 Spearman correlations between adherence and cognitive functioning

	AVLT learning	AVLT delay	MIST	LNS	SDMT	WCST	Stroop
Retrospective self-report	-.13	-.17	-.28*	-.03	-.10	.03	-.06
Prospective self-report	-.27	-.29*	-.38**	-.18	-.16	-.06	-.22
Electronic monitoring	-.32*	-.34*	-.31*	-.12	-.14	-.24	-.12
Diary records	-.39**	-.41**	-.28*	-.09	-.14	-.25	-.14

* = $P < .05$, ** = $P < .01$

AVLT Auditory Verbal Learning Test, MIST Memory for Intentions Screening Test (prospective memory), LNS Letter Number Sequencing, SDMT Symbol Digit Modalities Test, WCST Wisconsin Card Sorting Test

($r = .32$, $P < .05$), increased openness ($r = .36$, $P < .01$), and decreased conscientiousness ($r = -.47$, $P < .001$). Worse prospective self-reported memory and adherence as measured by medication diaries were also associated with decreased conscientiousness ($r = -.31$, $P < .05$ and $r = -.35$, $P < .05$, respectively).

Cognition and adherence

As illustrated in Table 3, worse retrospective self-reported adherence was associated with worse prospective memory as measured by the Memory for Intentions Screening Test ($r = -.28$, $P < .05$). Worse prospective self-reported adherence was associated with poorer delayed list recall ($r = -.29$, $P < .05$) and worse performance on the Memory for Intentions Screening Test ($r = -.38$, $P < .01$). Similarly, poorer adherence as measured by electronic monitoring and diary records was associated

with worse Memory for Intentions Screening Test ($r = -.31$, $P < .05$ and $r = -.28$, $P < .05$, respectively), list learning ($r = -.32$, $P < .05$ and $r = -.39$, $P < .01$, respectively), and delayed list recall ($r = -.34$, $P < .05$ and $r = -.41$, $P < .01$, respectively) performance.

Between group analyses

Table 4 examines emotional, personality, and memory differences between variable/poor (>10% missed) and good/adequate adherers (<10% missed). Variable/poor adherers were less conscientiousness and more depressed, anxious, fatigued, and neurotic than adequate/good adherers. Similarly, patients with at least one mental illness were significantly more likely to be variable/poor adherers ($\chi^2(1, N = 55) = 14.12$, $P < .001$). Nearly 63% of patients with at least one current mood and/or anxiety disorder diagnosis were variable/poor adherers; in contrast, only

Table 4 Between group analyses for emotion, personality, and memory variables

	Adequate/good adherence (<10% missed)		Variable/poor adherence (>10% missed)		t (df)	P
	Mean	SD	Mean	SD		
Emotion						
BDI	2.38	2.71	4.87	3.48	2.80(20.72)	<.05
STAI	38.35	9.53	46.73	11.40	2.75(53)	<.01
MFIS	8.68	3.73	11.00	4.42	1.95(53)	<.10
Memory						
MIST	5.09	1.02	4.13	1.19	2.90(51)	<.01
AVLT Learning	27.33	6.12	26.07	5.89	.69(53)	n.s.
AVLT Delay	8.25	3.13	7.00	2.70	1.37(53)	n.s.
Personality						
NEO-C	49.05	9.70	35.67	9.30	4.61(53)	<.001
NEO-N	48.65	9.24	57.00	11.59	2.78(53)	<.01
NEO-O	44.52	9.00	49.67	12.57	1.69(53)	<.10
NEO-A	51.63	13.56	47.00	9.78	1.21(53)	n.s.
NEO-E	48.48	9.24	48.46	11.49	1.00(53)	n.s.

BDI Beck Depression Inventory-Fast Screen, STAI Trait subscale of the State Trait Anxiety Inventory, MFIS Modified Fatigue Impact Scale, MIST Memory for Intentions Screening Test, AVLT Auditory Verbal Learning Test, NEO-C Conscientiousness Scale of the NEO-FFI, NEO-N Neuroticism scale of the NEO-FFI, NEO-O Openness scale of the NEO-FFI, NEO-A Agreeableness Scale of the NEO-FFI, NEO-E Extroversion scale of the NEO-FFI

12.8% of patients who did not meet criteria for a psychiatric illness exhibited variable/poor adherence.

Variable/poor adherers also exhibited poorer performance on a test of prospective memory. In contrast to Spearman correlations which found a consistent relationship between prospective measures of adherence and list learning, no between group differences emerged between variable/poor adherers and adequate/good adherers on a list learning task. To further explore this discrepancy, we examined how poor adherers (>20% missed, $n = 10$) performed on the task compared to the rest of the sample (<20% missed, $n = 45$). Poor adherers (mean = 6.20 ± 2.44) recalled fewer words after a delay than the rest of the sample (mean = 8.29 ± 3.06 ; $t(53) = 2.09$, $P < .05$). Adherence subgroups did not differ significantly by age, sex, education, disability status, diagnosis duration, or length of disease modifying therapy use.

Discussion

This is the first study to prospectively and objectively examine the association between long-term adherence to disease modifying therapies and common neuropsychiatric symptoms of MS. Results supported a strong link between treatment adherence and MS patients' emotional functioning. Nearly 63% of MS patients with a current mood or anxiety disorder exhibited variable or poor adherence over the course of the study. These patients were almost 5 times as likely as MS patients with no psychiatric diagnosis to exhibit problems adhering to their disease modifying therapies. Variable/poor adherers also endorsed more mood and anxiety symptoms via self-report than patients with adequate adherence during the course of the study. As a majority of MS patients experience psychiatric illness during their lifetimes, results highlight the importance of thorough assessment and treatment of mood and anxiety disorders in MS. Special care should be given to regularly assess adherence to disease modifying therapies among MS patients with psychiatric illness.

Personality traits were also associated with adherence. Adequate/good adherers were significantly more conscientious than variable/poor adherers. People who are conscientious are more likely to be punctual and organized. This finding has potential implications for the treatment of poor adherence in MS. One aspect of treatment may involve teaching participants about the importance of structure and organization when taking disease modifying therapies. Variable/poor adherers were also more neurotic than adequate/good adherers, further reinforcing the importance of psychiatric and psychological treatment of mental illness to ensure appropriate treatment adherence in MS. In addition to these between-group findings, continuous analyses

demonstrated that self-reported retrospective adherence was significantly associated with the openness. Patients with increased openness were more likely to report adherence problems at the outset of the study. This finding highlights the importance of objective, prospective monitoring of adherence, as personality variables may play a role in determining whether patients report adherence difficulties. MS patients who are less open may feel uncomfortable talking candidly about their adherence problems with treating physicians.

Memory difficulties were also associated with poor adherence. Variable/poor adherers performed significantly worse on a test of prospective memory than patients with adequate/good adherence. Poor adherers also performed worse than the rest of the sample on a delayed list recall task. Similarly, continuous analyses showed that performance on memory tasks was consistently associated with prospective measures of adherence and prospective memory was associated with all adherence measures. These findings are consistent with MS patient reports of "forgetting" as a common cause of improper medication management. Contrary to expectations, adherence was not associated with performance on tests of processing speed, attention, or executive functioning.

Findings from the current study reinforce the importance of using multiple measures in MS adherence research, including at least one measure of prospectively recorded objective adherence. Retrospective self-report of adherence was significantly associated with several emotional and personality variables that were not significantly associated with prospective, objective measures. This is consistent with previous research suggesting that retrospective self-report may overestimate adherence (Inui et al. 1981; Liu et al. 2001; Zeller et al. 2008). It may be that self-report of adherence is influenced by emotional and personality factors that distort patients' perceptions of their true adherence. Nevertheless, assessing self-reported adherence remains standard clinical practice. In conjunction with objective prospective measures, future studies should continue to assess self-reported adherence to increase ecological validity and allow comparisons to previous research.

The current study differs in several ways from the majority of previous adherence research in MS. Previous studies have largely relied on retrospective reports of adherence or treatment discontinuation. Only one study has prospectively examined long-term adherence to disease modifying therapies in MS (Turner et al. 2007). In this study, poor medication adherence was associated with a lack of perceived benefit. In contrast to the present findings, medication adherence was not consistently associated with memory. These discrepant results could be due to methodological and sampling differences. Unlike the

Turner et al. study, the current study employed objective methods of adherence measurement in a sample of largely female MS patients.

Despite robust findings, the primary limitation of the present study is the relatively small sample size. Future studies should employ extended objective adherence monitoring in a large sample of MS patients. Future studies should also examine the association between adherence and relapse rates in a diverse sample of patients that uses a representative mix of disease modifying therapies. Finally, the study employed a correlational design that limits our ability to make causal assumptions. Though it may seem likely that emotional, cognitive, and personality disturbance influence treatment adherence, it is also possible that poor treatment adherence causes quickened disease progression, which in turn causes the aforementioned neuropsychiatric symptoms. Strengths of the current study include the use of a comprehensive battery that included objective measures of cognitive function, a thorough psychiatric interview, and validated self-report measures. Additional strengths include the use of retrospective and prospective adherence measures, including objective electronic monitoring and diary records.

In summary, this is the first study to employ objective adherence monitoring to prospectively examine the association between neuropsychiatric symptoms and patterns of long-term medication use in MS. MS patients with a current mood and/or anxiety disorder were five times more likely to have suspect adherence. Poor adherence was associated with memory difficulties, anxiety, depression, neuroticism, and reduced conscientiousness. Results highlight the importance of conducting a thorough psychiatric and neuropsychological evaluation when patients have problems taking their medications as prescribed. Findings suggest that pharmacological or psychotherapeutic treatment of mood/anxiety disorders, use of scheduled reminders, and/or increased organization and structure may lead to improved adherence in MS.

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